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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number:
A61K 31/41, 31/42, 31/425, 31/44, 31/495, 31/505	A1	WO 95/07694
		(43) International Publication Date: 23 March 1995 (23.03.95)

(21) International Application Number: PCT/US94/10389

(22) International Filing Date: 14 September 1994 (14.09.94)

(30) Priority Data:

08/122,251	15 September 1993 (15.09.93)	US
08/293,899	23 August 1994 (23.08.94)	US

(81) Designated States: AU, CA, CN, CZ, FI, HU, JP, KR, MW, NO, NZ, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

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(54) Title: USE OF THIAZOLIDINEDIONES TO PREVENT OR DELAY ONSET OF NIDDM

(57) Abstract

Novel methods of using thiazolidinone derivatives and related antihyperglycemic agents to treat populations experiencing impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus (NIDDM) and complications arising thereform are disclosed.

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USE OF THIAZOLIDINEDIONES TO PREVENT OR DELAY ONSET OF NIDDM

FIELD OF THE INVENTION

The present invention pertains to a number of compounds which can be used to treat impaired glucose intolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus (NIDDM). More specifically, the present invention involves in one embodiment administering to a patient certain known thiazolidinedione derivatives and related antihyperglycemic agents which reduce fasting insulin levels and return normal glucose tolerance to an individual, thus preventing or delaying the onset of NIDDM or complications resulting therefrom.

BACKGROUND

Diabetes is one of the most prevalent chronic disorders worldwide with significant personal and financial costs for patients and their families, as well as for society. Different types of diabetes exist with distinct etiologies and pathogeneses. For example, diabetes mellitus is a disorder of carbohydrate metabolism, characterized by hyperglycemia

and glycosuria and resulting from inadequate production or utilization of insulin.

Diabetes mellitus often develops from certain at risk populations, one such population is individuals with impaired glucose tolerance (IGT). Impaired glucose tolerance is a condition intermediate between frank, noninsulin-dependent diabetes mellitus and normal glucose tolerance in which the affected person's postprandial glucose response is abnormal as assessed by 2-hour postprandial plasma glucose levels. This IGT population progresses to a certain form of diabetes mellitus, specifically noninsulin-dependent diabetes mellitus (NIDDM).

NIDDM or otherwise referred to as Type II diabetes is the form of diabetes mellitus which occurs predominantly in adults in whom adequate production of insulin is available for use, yet a defect exists in insulin-mediated utilization and metabolism of glucose in peripheral tissues. It has been shown that for some people with diabetes a genetic predisposition results in a mutation in the gene(s) coding for insulin and/or the insulin receptor and/or insulin-mediated signal transduction factor(s), thereby resulting in ineffective insulin and/or insulin-mediated effects thus impairing the utilization or metabolism of glucose. The population with impaired glucose tolerance progresses to NIDDM at a rate of 5% to 10% of cases per year.

Failure to treat NIDDM can result in mortality due to cardiovascular disease and in other diabetic complications including retinopathy, nephropathy, and peripheral neuropathy. For many years treatment of NIDDM has involved a program aimed at lowering blood sugar with a combination of diet and exercise. Alternatively, treatment of NIDDM involved oral hypoglycemic agents, such as sulfonylureas alone or in

combination with insulin injections. Recently, alpha-glucosidase inhibitors, such as acarbose, have been shown to be effective in reducing the postprandial rise in blood glucose (Lefevre, et al., Drugs 1992;44: 29-38). In Europe and Canada another treatment used primarily in obese diabetics is metformin, a biguanide.

In any event, what is required is a method of treating populations experiencing impaired glucose tolerance in order to prevent or delay the onset of NIDDM thereby bringing relief of symptoms, improving the quality of life, preventing acute and long-term complications, reducing mortality and treating accompanying disorders of those at risk for NIDDM. The methods of using the disclosed compounds for treating populations experiencing impaired glucose tolerance to prevent or delay the onset of NIDDM as taught herein meet these objectives.

Compounds useful for practicing the present invention, and methods of making these compounds are known. Some of these compounds are disclosed in WO 91/07107; WO 92/02520; WO 94/01433; WO 89/08651; JP Kokai 69383/92; U.S. Patent Nos. 4,287,200; 4,340,605; 4,438,141; 4,444,779; 4,461,902; 4,572,912; 4,687,777; 4,703,052; 4,725,610; 4,873,255; 4,897,393; 4,897,405; 4,918,091; 4,948,900; 5,002,953; 5,061,717; 5,120,754; 5,132,317; 5,194,443; 5,223,522; 5,232,925; and 5,260,445. The active compounds disclosed in these publications are useful as therapeutic agents for the treatment of diabetes, hyperglycemia, hypercholesterolemia, and hyperlipidemia. The disclosure of these publications are incorporated herein by reference in particular with respect to the active compounds disclosed therein, and methods of preparation thereof. These compounds are useful for the treatment of impaired glucose tolerance (IGI) in order to prevent or delay onset of NIDDM and complications resulting therefrom, in accordance with the present invention.

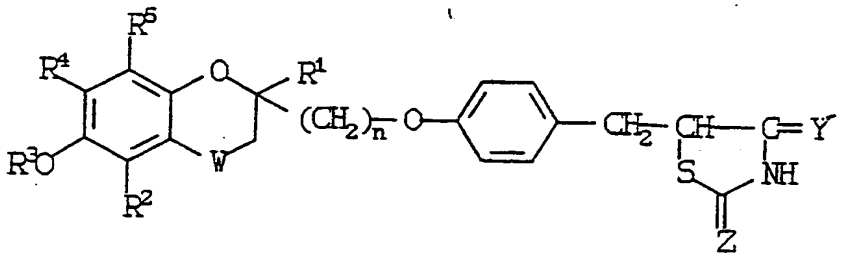
There is no disclosure in the above-identified references to use the compounds identified in this present application in the treatment of populations experiencing impaired glucose tolerance in order to prevent or delay the onset of NIDDM and complications resulting therefrom.

SUMMARY OF THE INVENTION

The present invention provides a method for the treatment of impaired glucose tolerance in order to prevent or delay the onset of NIDDM. It is known that persons with impaired glucose tolerance have a much higher rate of progression to NIDDM than persons with normal glucose tolerance. Saad, et al., New Engl J Med 1988; 319:1500-6. If impaired glucose tolerance can be normalized, it is likely that the progression to NIDDM will be delayed or prevented in this population.

Compounds useful for practicing the present invention reduce fasting insulin levels, improve insulin sensitivity, and return glucose tolerance to the normal range for many individuals. As agents having the aforementioned effects (in the return of glucose tolerance), the compounds of the following formulas are useful in prophylactically treating individuals to prevent or delay the onset of NIDDM.

Accordingly, the present invention is the use of compounds of Formula I



I

wherein R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1-C_8 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1-C_8 alkoxy)carbonyl group, or an aralkyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, or R^4 and R^5 together represent a C_1-C_4 alkylenedioxy group;

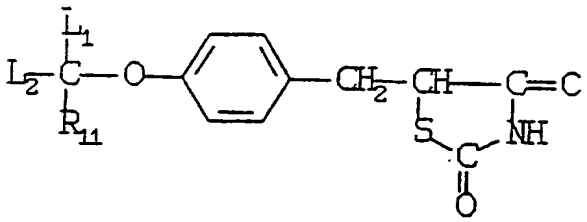
n is 1, 2, or 3;

W represents the $-CH_2-$, >CO, or CH-OR^6 group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

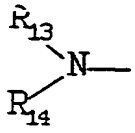
and pharmaceutically acceptable salts thereof.

The present invention is also the use of compounds of the Formula II



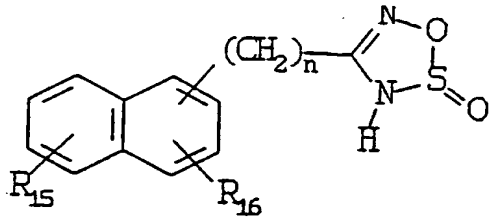
II

wherein R_{11} is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula



wherein R_{13} and R_{14} are the same or different and each is lower alkyl or R_{13} and R_{14} are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring;
wherein R_{12} means a bond or a lower alkylene group; and
wherein L_1 and L_2 are the same or different and each is hydrogen or lower alkyl or L_1 and L_2 are combined to form an alkylene group; or a pharmaceutically acceptable salt thereof.

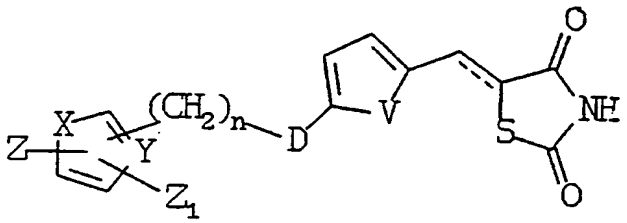
The present invention is also the use of compounds of the Formula III



III

wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methylthio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof.

The present invention is also directed to the use of compounds of the Formula IV

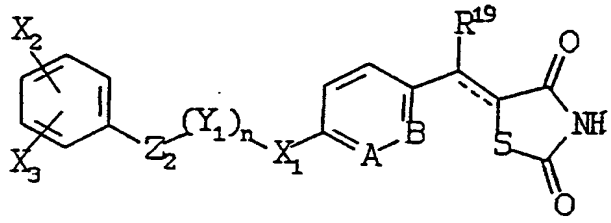


IV

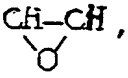
wherein the dotted line represents a bond or no bond;
V is -CH = CH-, -N = CH-, -CH = N- or S;
D is CH_2, CHOH, CO, C = NOR_{17} or CH = CH;
X is S, O, NR_{18}, -CH = N or -N = CH;
Y is CH or N;
Z is hydrogen, (C_1-C_7) alkyl, (C_3-C_7)cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, or phenyl mono- or disubstituted with the same or different groups which are (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, fluoro, chloro, or bromo;
Z_1 is hydrogen or (C_1-C_3)alkyl;
R_{17} and R_{18} are each independently hydrogen or methyl; and
n is 1, 2, or 3;

the pharmaceutically acceptable cationic salts thereof; and the pharmaceutically acceptable acid addition salts thereof when the compound contains a basic nitrogen.

The present invention is also directed to the use of compounds of the Formula V

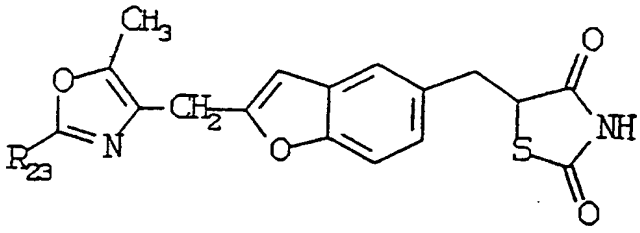


V

wherein the dotted line represents a bond or no bond;
A and B are each independently CH or N, with the proviso that when A or B is N, the other is CH;
X_1 is S, SO, SO_2, CH_2, CHOH, or CO;
n is 0 or 1;
Y_1 is CHR_{20} or R_{21}, with the proviso that when n is 1 and Y_1 is NR_{21}, X_1 is SO_2 or CO;
Z_2 is CHR_{22}, CH_2CH_2, CH=CH,  ,

OCH_2, SCH_2, $SOCH_2$ or SO_2CH_2;
R_{19}, R_{20}, R_{21}, and R_{22} are each independently hydrogen or methyl; and
X_2 and X_3 are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phenoxy, benzyloxy, bromo, chloro, or fluoro;
a pharmaceutically acceptable cationic salt thereof; or
a pharmaceutically acceptable acid addition salt thereof when A or B is N.

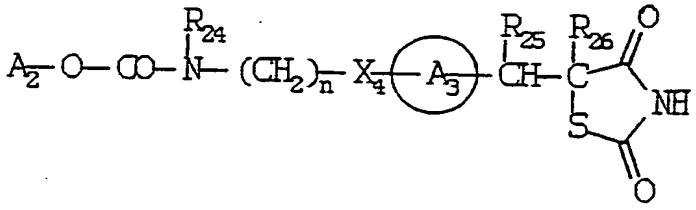
The present invention also relates to the use of compounds of the Formula VI



VI

or a pharmaceutically acceptable salt thereof wherein R_{23} is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl or mono- or di-substituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl.

The present invention also provides the use of a compound of Formula VII



VII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_2 represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

A_3 represents a benzene ring having in total up to 3 optional substituents;

R_{24} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or A_2 together with R_{24} represents substituted or unsubstituted C_{2-3} polymethylene group, optional substituents for the

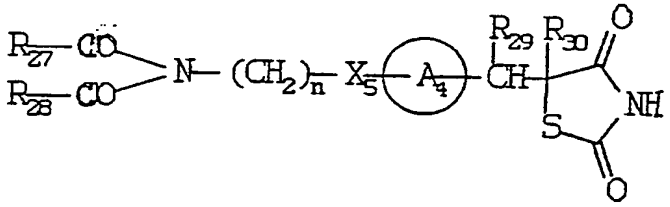
polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

R_{25} and R_{26} each represent hydrogen, or R_{25} and R_{26} together represent a bond;

X_4 represents O or S; and

n represents an integer in the range of from 2 to 6.

The present invention also provides the use of a compound of Formula VIII



VIII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate therefor, wherein:

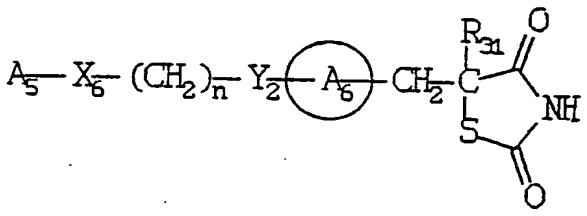
R_{27} and R_{28} each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group being substituted or unsubstituted in the aryl or alkyl moiety; or R_{27} together with R_{28} represents a linking group, the linking group consisting of an optionally substituted methylene group and either a further optionally substituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected from alkyl-, aryl, or aralkyl, or substituents of adjacent methylene groups together with the carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

R_{29} and R_{30} each represent hydrogen, or R_{29} and R_{30} together represent a bond;

A_4 represents a benzene ring having in total up to 3 optional substituents;

X_5 represents O or S; and
n represents an integer in the range of from 2 to 6.

The present invention also provides the use of a compound of Formula IX



IX

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:
A_5 represents a substituted or unsubstituted aromatic heterocyclyl group;
A_6 represents a benzene ring having in total up to 5 substituents;
X_6 represents O, S, or NR_{32} wherein R_{32} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
Y_2 represents O or S;
R_{31} represents an alkyl, aralkyl, or aryl group; and
n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur, or nitrogen.

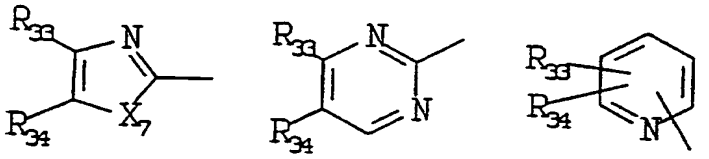
Favored aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl group comprises 1, 2, or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur, or nitrogen.

Suitable values for A_5 when it represents a 5-membered aromatic heterocyclyl group include thiazolyl and oxazoyl, especially oxazoyl.

Suitable values for A_5 when it represents a 6-membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

Suitable R_{31} represents an alkyl group, in particular a C_{1-6} alkyl group, for example a methyl group. Preferably, A_5 represents a moiety of formula (a), (b), or (c):

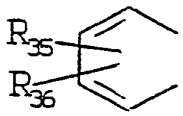


(a) (b) (c)

wherein:

R_{33} and R_{34} each independently represents a hydrogen atom, an alkyl group, or a substituted or unsubstituted aryl group or when R_{33} and R_{34} are each attached to adjacent carbon atoms, then R_{33} and R_{34} together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R_{33} and R_{34} together may be substituted or unsubstituted; and in the moiety of Formula (a), X_7 represents oxygen or sulphur.

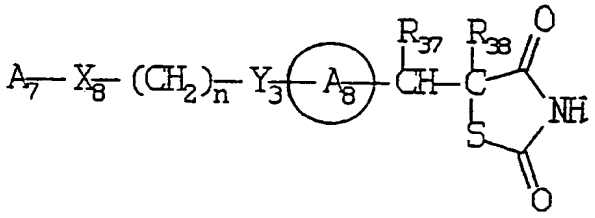
In one favored aspect R_{33} and R_{34} together represent a moiety of Formula (d):



(d)

wherein R_{35} and R_{36} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl, or alkoxy.

The present invention also provides for the use of compounds for Formula X



X

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_7 represents a substituted or unsubstituted aryl group;

A_8 represents a benzene ring having in total up to 5 substituents;

X_8 represents O, S, or NR_{39} wherein R_{39} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

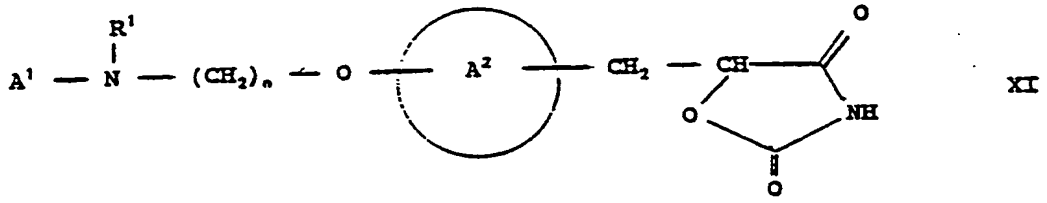
Y_3 represents O or S;

R_{37} represents hydrogen;

R_{38} represents hydrogen or an alkyl, aralkyl, or aryl group or R_{37} together with R_{38} represents a bond; and

n represents an integer in the range of from 2 to 6.

The present invention is also directed to the use of compounds of the Formula



XI

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:
A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;
R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
A^2 represents a benzene ring having in total up to five substituents; and
n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

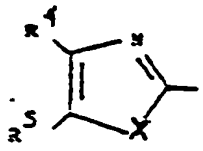
Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

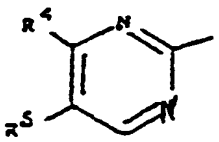
Suitable values for A^1 when it represents 5-membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

Suitable values for A^1 when it represents a 6-membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

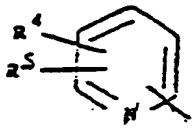
Preferably, A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



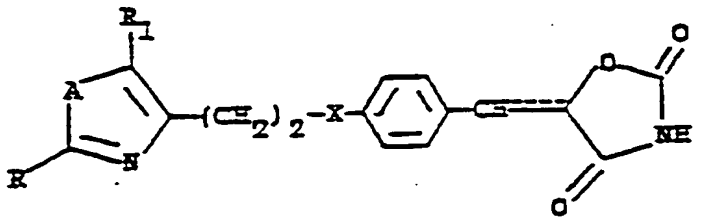
(c)

wherein:

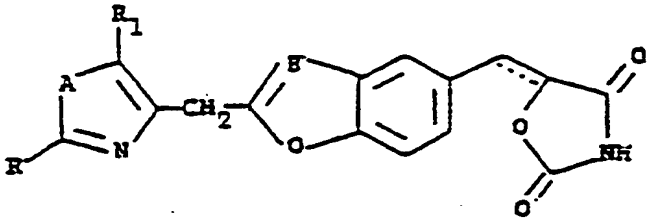
R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to adjacent carbon atoms, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a)

X represents oxygen or sulphur.

The present invention is also directed to the use of compounds of the Formulas



XII



XIII

or a pharmaceutically acceptable salt thereof wherein the dotted line represents a bond or no bond; R is cycloalkyl of three to seven carbon atoms, naphthyl, thienyl, furyl, phenyl or substituted phenyl wherein said substituent is alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms, trifluoromethyl, chloro, fluoro or bis(trifluoromethyl); R_1 is alkyl of one to three carbon atoms; X is O or C=O; a is O or S; and B is N or CH.

A preferred group of compounds are those of formula XI wherein the dotted line represents no bond, R_1 is methyl, X is O and A is O. Especially preferred within this group are the compounds where R is phenyl, 2-naphthyl and 3,5-bis(trifluoromethyl)phenyl.

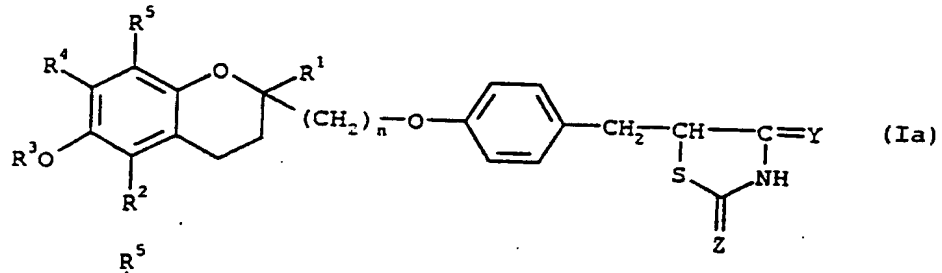
A second group of preferred compounds are those of formula XII wherein the dotted line represents no bond, R_1 is methyl and A is O. Especially preferred within this group are compounds where B is CH and R is phenyl, p-tolyl, m-tolyl, cyclohexyl and 2-naphthyl. Also especially preferred is the compound where B is N and R is phenyl.

A still further embodiment of the present invention is the use of pharmaceutical composition for administering an effective amount of a compound of

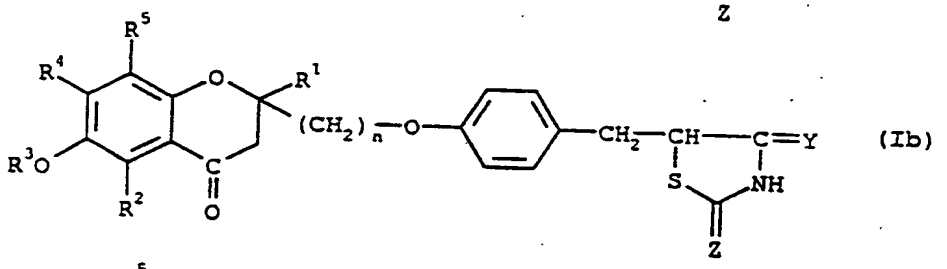
the preceding Formulas I through XIII along with a pharmaceutically acceptable carrier in unit dosage form in the treatment methods mentioned above.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

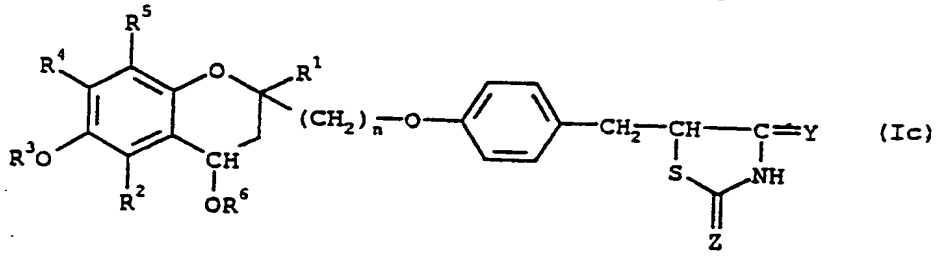
The compounds used in the treatment methods of the invention, which are 5-[4-(chromoanalkoxy)benzyl]-thiazolidene derivatives, may be represented by the Formulas (Ia), (Ib), and (Ic)



(Ia)



(Ib)



(Ic)

(in which R^1, R^2, R^3, R^4, R^5, R^6, n, Y, and Z are as defined above) and include pharmaceutically acceptable salts thereof.

In the compounds of the invention, where R^1 or R^2 represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 5 carbon

atoms and is preferably a primary or secondary alkyl group, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or isopentyl group.

Where R^3, R^6, or $R^{6'}$ represents an aliphatic acyl group, this preferably has from 1 to 6 carbon atoms and may include one or more carbon-carbon double or triple bonds. Examples of such groups include the formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, hexanoyl, acryloyl, methacryloyl, and crotonyl groups.

Where R^3, R^6, or $R^{6'}$ represents an alicyclic acyl group, it is preferably a cyclopentanecarbonyl, cyclohexanecarbonyl, or cycloheptanecarbonyl group.

Where R^3, R^6, or $R^{6'}$ represents an aromatic acyl group, the aromatic moiety thereof may optionally have one or more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such aromatic acyl groups included the benzoyl, p-nitrobenzoyl, m-fluorobenzoyl, o-chlorobenzoyl, p-aminobenzoyl, m-(dimethylamino)-benzoyl, o-methoxybenzoyl, 3,4-dichlorobenzoyl, 3,5-di-t-butyl-4-hydroxybenzoyl, and 1-naphthoyl groups.

Where R^3, R^6, or $R^{6'}$ represents a heterocyclic acyl group, the heterocyclic moiety thereof preferably has one or more, preferably one, oxygen, sulfur, or nitrogen hetero atoms and has from 4 to 7 ring atoms; examples of such heterocyclic acyl groups include the 2-furoyl, 3-thenoyl, 3-pyridinecarbonyl (nicotinoyl), and 4-pyridinecarbonyl groups.

Where R^3, R^6, or $R^{6'}$ represents an araliphatic acyl group, the aliphatic moiety thereof may optionally have one or more carbon-carbon double or triple bonds and the aryl moiety thereof may optionally have one or more substituents (for example, nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy substituents); examples of such araliphatic acyl groups

include the phenylacetyl, p-chlorophenylacetyl, phenylpropionyl, and cinnamoyl groups.

Where R^3, R^6, or $R^{6'}$ represents a (C_1-C_6 alkoxy)carbonyl group, the alkyl moiety thereof may be any one of those alkyl groups as defined for R^1 and R^2, but is preferably a methyl or ethyl group, and the alkoxycarbonyl group represented by R^3, R^6, or $R^{6'}$ is therefore preferably a methoxycarbonyl or ethoxycarbonyl group.

Where R^3, R^6, or $R^{6'}$ represents an aralkyloxycarbonyl group, the aralkyl moiety thereof may be any one of those included within the araliphatic acyl group represented by R^3, R^6, or $R^{6'}$, but is preferably a benzyloxycarbonyl group.

Where R^4 and R^5 represent alkyl groups, they may be the same or different and may be straight or branched chain alkyl groups. They preferably have from 1 to 5 carbon atoms and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and isopentyl groups.

Where R^4 and R^5 represent alkoxy groups, these may be the same or different and may be straight or branched chain groups, preferably having from 1 to 4 carbon atoms. Examples include the methoxy, ethoxy, propoxy, isopropoxy, and butoxy groups. Alternatively, R^4 and R^5 may together represent a C_1-C_4 alkylenedioxy group, more preferably a methylenedioxy or ethylenedioxy group.

Preferred classes of compounds of Formula I are as follows:

(1) Compounds in which R^3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an aromatic acyl group, or a heterocyclic acyl group.

(2) Compounds in which Y represents an oxygen atom; R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; R^3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an aromatic

acyl group, or a pyridinecarbonyl group; and R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group, or a C_1 or C_2 alkoxy group.

(3) Compounds as defined in (2) above, in which: R^1, R^2, R^4, and R^5 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; n is 1 or 2; and W represents the $-CH_2-$ or >CO group.

(4) Compounds as defined in (3) above, in which R^3 represents a hydrogen atom, a C_1-C_5 aliphatic acyl group, a benzoyl group, or a nicotinyl group.

(5) Compounds as defined in (4) above, in which: R^1 and R^4 are the same or different and each represents a C_1-C_5 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents a hydrogen atom or a C_1-C_4 aliphatic acyl group.

(6) Compounds in which: W represents the $-CH_2-$ or >CO group; Y and Z both represent oxygen atoms; n is 1 or 2; R^1 and R^4 are the same or different and each represents a C_1-C_4 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents a hydrogen atom or a C_1-C_4 aliphatic acyl group.

(7) Compounds as defined in (6) above, in which n is 1.

(8) Compounds as defined in (6) or (7) above, in which W represents the $-CH_2-$ group.

Preferred compounds among the compounds of Formula I are those wherein:

R^1 is a C_1-C_4 alkyl group, more preferably a methyl or isobutyl group, most preferably a methyl group;

R^2 is a hydrogen atom or a C_1-C_4 alkyl group, preferably a hydrogen atom, or a methyl or isopropyl group, more preferably a hydrogen atom or a methyl group, most preferably a methyl group;

R^3 is a hydrogen atom, a C_1-C_4 aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group, preferably a hydrogen atom, or an acetyl, butyryl, benzoyl, or nicotinyl group, more preferably a hydrogen atom or an acetyl, butyryl or benzoyl group, most preferably a hydrogen atom or an acetyl group;

R^4 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a methyl, isopropyl, t-butyl, or methoxy group, more preferably a methyl or t-butyl group, most preferably a methyl group;

R^5 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a hydrogen atom, or a methyl or methoxy group, more preferably a hydrogen atom or a methyl group, and most preferably a methyl group;

n is 1 or 2, preferably 1;

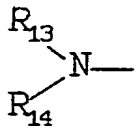
Y is an oxygen atom;

Z is an oxygen atom or an imino group, most preferably an oxygen atom; and

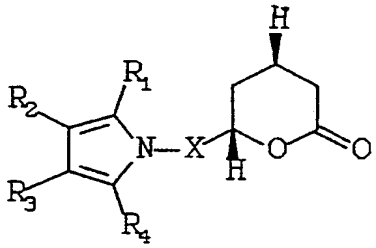
W is a $-CH_2-$ or $>C=O$ group, preferably a $-CH_2-$ group.

Referring to the general Formula II, the substituents may be any from 1 to 3 selected from nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl, or hydroxy, the aromatic acyl group may be benzoyl and naphthoyl. The alkyl group R_{11} may be a straight chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl; the cycloalkyl group R_{11} may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl; and the phenylalkyl group R_{11} may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R_{11} may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms

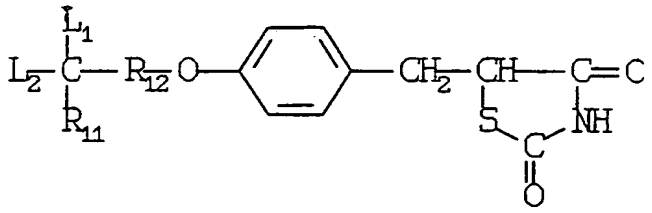
selected from among nitrogen, oxygen, and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R_{11} is



the lower alkyls R_{13} and R_{14} may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, and n-butyl. When R_{13} and R_{14} are combined to each other to form a 5- or 6-membered heterocyclic group as taken together with the adjacent N atom, i.e., in the form of

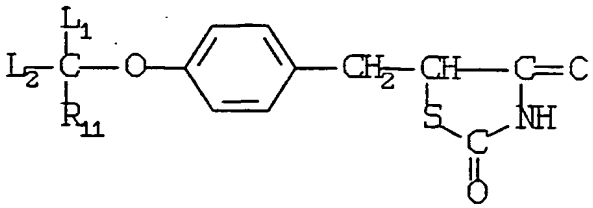


this heterocyclic group may further include a heteroatom selected from among nitrogen, oxygen, and sulfur as exemplified by piperidino, morpholino, pyrrolidino, and piperazino. The lower alkylene group R_{12} may contain 1 to 3 carbon atoms and thus may be, for example, methylene, ethylene, or trimethylene. The bond R_{12} is equivalent to the symbol "-", ".", or the like which is used in chemical structural formulas, and when R_{12} represents such a bond, the compound of general Formula II is represented by the following general Formula II(a)



II(a)

Thus, when R_{12} is a bond, the atoms adjacent thereto on both sides are directly combined together. As examples of the lower alkyls L_1 and L_2, there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L_1 and L_2 are joined together is a group of the formula $-(CH_2)_n-$ [where n is an integer of 2 to 6]. The cycloalkyl, phenylalkyl, phenyl, and heterocyclic groups mentioned above, as well as said heterocyclic group



may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.), and hydroxyl. The case also falls within the scope of the general Formula II that an alkylenedioxy group of the formula $-O-(CH_2)_m-O-$ [is an integer of 1 to 3], such as methylene-dioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

The preferred compounds of Formula III are those wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile,

trifluoromethyl, vinyl, or nitro; n is 1 or 2 and the pharmaceutically acceptable salts thereof.

Preferred in Formula IV are compounds wherein the dotted line represents no bond, particularly wherein D is CO or CHOH. More preferred are compounds wherein V is -CH = CH-, -CH = N- or S and n is 2, particularly those compounds wherein X is O and Y is N, X is S and Y is N, X is S and Y is CH or X is -CH = N- and Y is CH. In the most preferred compounds X is O or S and Y is N forming an oxazol-4-yl, oxazol-5-yl, thiazol-4-yl, or thiazol-5-yl group; most particularly a 2-[(2-thienyl), (2-furyl), phenyl, or substituted phenyl]-5-methyl-4-oxazolyl group.

The preferred compounds in Formula V are:

a) those wherein the dotted line represents no bond, A and B are each CH, X_1 is CO, n is 0, R_{19} is hydrogen, Z_2 is CH_2CH_2 or CH=CH and X_3 is hydrogen, particularly when X_2 is hydrogen, 2-methoxy, 4-benzyloxy, or 4-phenyl;

b) those wherein A and B are each CH, X_1 is S or SO_2, n is 0, R_{19} is hydrogen, Z_2 is CH_2CH_2 and X_3 is hydrogen, particularly when X_2 is hydrogen or 4-chloro.

A preferred group of compounds is that of Formula VI wherein R_{23} is (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, phenyl, halophenyl, or (C_1-C_6)alkylphenyl. Especially preferred within this group are the compounds where R_{23} is phenyl, methylphenyl, fluorophenyl, chlorophenyl, or cyclohexyl.

When used herein with regard to Formulas VII through X, the term "aryl" includes phenyl and naphthyl, suitably phenyl, optionally substituted with up to 5, preferably up to 3, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

The term "halogen" refers to fluorine, chlorine, bromine, and iodine; preferably chlorine.

The terms "alkyl" and "alkoxy" relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

Suitable alkyl groups are C_{1-12} alkyl groups, especially C_{1-6} alkyl groups, e.g., methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of alkyl, alkoxy, aryl, and halogen or any 2 substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said 2 substituents may themselves be substituted or unsubstituted.

Specific examples of compounds of the present invention are given in the following list:

(+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl]methyl]-2,4-thiazolidinedione: (troglitazone);

4-(2-naphthylmethyl)-1,2,3,5-oxathiadiazole-2-oxide;

5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]-benzyl]-5-methylthiazolidine-2,4-dione;

5-[4-[2-[2,4-dioxo-5-phenylthiazolidin-3-yl)ethoxy]-benzyl]thiazolidine-2,4-dione;

5-[4-[2-[N-methyl-N-(phenoxycarbonyl)amino]ethoxy]-benzyl]thiazolidine-2,4-dione;

5-[4-(2-phenoxyethoxy)benzyl]thiazolidine-2,4-dione;

5-[4-[2-(4-chlorophenyl)ethylsulfonyl]benzyl]-thiazolidine-2,4-dione;

5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiazolidine-2,4-dione;

5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiadiazolidine-2,4-dione: (ciglitazone);

5-[[4-(3-hydroxy-1-methylcyclohexyl)methoxy]benzyl]-thiadiazolidine-2,4-dione;

5-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxyl]-benzyl]thiadizolidione-2,4-dione;

5-[4-[2-(5-ethylpyridin-2-yl)ethoxyl]benzyl]-thiadiazolidine-2,4- dione: (pioglitazone);

5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]-thiadiazoline-2,4-dione: (englitazone);

5-[[2-(2-naphthylmethyl)benzoxazol]-5-ylmethyl]-thiadiazoline-2,4-dione;

5-[4-[2-(3-phenylureido)ethoxyl]benzyl]thiadiazoline-2,4-dione;

5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]-benzy]thiadiazoline-2,4-dione;

5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiadiazoline-2,4-dione;

5-[2-(5-methyl-2-phenyloxazol-4-ylmethyl)-benzofuran-5-ylmethyl]- oxazolidine-2,4-dione;

5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]-benzyl]thiazolidine-2,4-dione; and

5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]-benzyl]- oxazolidine-2,4-dione.

As defined herein, "complications of NIDDM" is referred to as cardiovascular complications or several of the metabolic and circulatory disturbances that are associated with hyperglycemia, e.g., insulin resistance, hyperinsulinemia and/or hyperproinsulinemia, delayed insulin release, dyslipidemia, retinopathy, peripheral neuropathy, nephropathy, and hypertension.

The compounds of Formulas I through XIII are capable of further forming pharmaceutically acceptable base salts.

The compounds of Formulas I through XIII are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formulas I through XIII include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate, n-methyl glucamine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and

isolating the free base in the conventional manner or as above. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science 1977;66:1-19).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner or as above. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in different configurations. The compounds can, therefore, form stereoisomers. Although these are all represented herein

by a limited number of molecular formulas, the present invention includes the use of both the individual, isolated isomers and mixtures, including racemates, thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials in the preparation of the compounds, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques, or the mixture may be used as it is, without resolution.

Furthermore, the thiazolidene or oxazolidene part of the compounds of Formulas I through XIII can exist in the form of tautomeric isomers. All of the tautomers are represented by Formulas I through XIII, and are intended to be a part of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch,

gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions.

These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use in the treatment of at risk populations such as those with impaired glucose tolerance, to prevent or delay the onset of NIDDM and complications arising therefrom, the compounds utilized in the pharmaceutical methods of this invention are administered along with a pharmaceutically acceptable carrier at the initial dosage of about 0.01 mg to about 20 mg per kilogram daily. A daily dose range of about 0.01 mg to about 10 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter,

the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The compounds of Formulas I through XIII are valuable agents in returning an individual to a state of glucose tolerance and therefore preventing or delaying the onset of NIDDM. The following illustrates testing to show that compounds have the disclosed activity, using the preferred compound troglitazone.

EXAMPLE 1

In a blinded, randomized, fixed-dose, parallel-group, placebo-controlled, outpatient trial, the effects of the test compound, (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]-methyl]-2,4-thiazolidinedione (troglitazone), was compared with that of a placebo on glucose tolerance and on insulin sensitivity. The trial in impaired glucose tolerance (IGT) included a 2-week screening period and a 12-week treatment period. Fifty-six patients were randomized to treatment with placebo or 400 mg/day of troglitazone. Oral glucose tolerance tests (OGTT) and frequently sampled intravenous glucose tolerance tests (FSIGTT) to assess insulin sensitivity were performed before study medication, and after 6 weeks and after 12 weeks of randomized treatment.

Patients included in this study were adults in reasonably good health who have IGT by the WHO criteria as demonstrated by OGTT (Harris M.I., Hadden W.C., Knowler W.C., Berrett P.H., International Criteria for

the Diagnosis of Diabetes and Impaired Glucose Tolerance, Diabetes Care 1985;8(6):562-7). Most of the patients that were recruited were relatives of patients with NIDDM, patients with a history of gestational diabetes mellitus, patients with a history of prior abnormal OGTT, or patients with other indicators of insulin resistance (coronary artery disease, obesity, hypertriglyceridemia, and hypertension).

The OGTT was carried out according to the following procedure:

Test was administered in the morning after a 10- to 14-hour fast. Water, but not coffee, could be consumed during the fast. Patients were required to remain seated during the test. Study medication was omitted on the morning of the test and taken with lunch.

5 mL of venous blood was collected into a serum separation tube for baseline.

1.75-g/kg body weight, up to a maximum of 75 g of glucose was administered orally as a liquid beverage to be consumed over no more than 5 minutes.

5 mL of venous blood was collected into a serum separation tube every 30 minutes up to 2 hours, timing from the start of ingestion of the glucose.

Each blood specimen was allowed to clot for 30 minutes. The specimens were centrifuged until clot and serum were separated by a well-formed polymer barrier. Serum was transferred from each specimen, using separate pipettes for each, into plastic vials and frozen immediately. If centrifuging of specimens was delayed for any reason, specimens were refrigerated and centrifuged as soon as possible.

Frozen specimens were examined for oral glucose tolerance according to the WHO diagnostic criteria.

WHO Diagnostic Criteria

Serum Glucose mg/dL (mmol/L)	Normal	IGT	Diabetes
Fasting	<140 (<7.8)	<140 (<7.8)	≥140 (≥7.8)
2 hour	<140 (<7.8)	140-199 (7.8-11.1)	≥200 (≥11.1)

PROTOCOL 1

Treatment Effects

	2-Hour Glucose (mg/dL)		Fasting Insulin (UIU/mL)	
Test Compound A	Baseline	6 Week	Baseline	6 Week
1	167.00	81.00	14.40	2.00
2	143.00	146.00	9.10	25.70
3	143.00	106.00	4.00	6.20
4	167.00	85.00	12.70	11.30
5	166.00	113.00	13.20	13.30
6	158.00	101.00	20.00	11.30
7	148.00	81.00	8.30	2.00
8	166.00	172.00	21.80	9.30
9	187.00	158.00	22.50	12.20
10	147.00	98.00	12.00	7.70
Placebo				
1	182.00	155.00	20.70	17.20
2	154.00	125.00	10.30	10.90
3	145.00	155.00	12.30	12.10
4	160.00	133.00	25.90	11.60
5	184.00	177.00	27.70	20.20
6	160.00	193.00	23.90	50.30
7	144.00	145.00	5.50	8.60
8	148.00	132.00	15.40	12.20
9	181.00	229.00	18.10	27.70
10	170.00	141.00	19.80	13.50

The results of the OGTTs show that treatment with the test compound correlates to reduction of fasting insulin levels and return of glucose tolerance to the normal range for approximately 70% of the subjects. With the exception of one placebo-responder, treatment with placebo does not change significantly the fasting insulin and glucose tolerance profiles.

PROTOCOL 1

Summary of OGTT Glucose (mg/dL)

Treatment	Hour	Screening (N = 38)	Week 6 (N = 37)	Week 12 (N = 19)
Compound A	0	105	88	95
	0.5	173	153	157
	1.0	185	151	162
	1.5	170	145	152
	2.0	160	123	131
Placebo	0	102	100	99
	0.5	169	164	163
	1.0	184	191	186
	1.5	176	181	176
	2.0	162	155	150

These results show that the average value for 2-hour glucose from the OGTT returns to the normal range for patients treated for 6 weeks and 12 weeks with Test Compound A compared to placebo which shows no significant change in the average value for 2-hour glucose.

PROTOCOL 1

Conversion After 6 Weeks of Treatment From IGT to Normal by WHO Classification

Treatment	IGT at Screening	Converted to Normal
Compound A	18	12 (67%)
Placebo	19	7 (37%)

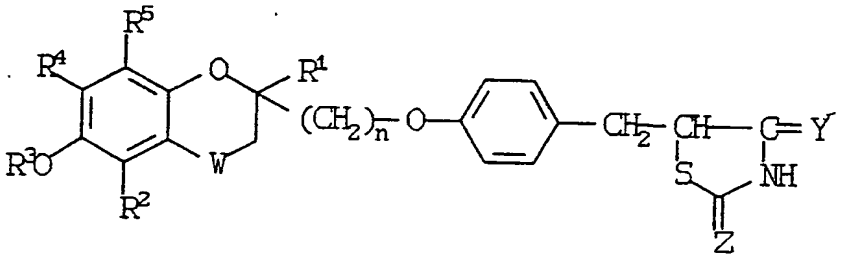
The results show that on a patient-by-patient analysis, significantly more persons classified with IGT convert to normal glucose tolerance after treatment with Test Compound A (67%) than with placebo (37%).

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are

to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:

1. A method of treating impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I:



I

wherein R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1-C_8 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1-C_8 alkoxy)carbonyl group, or an aralkyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, or R^4 and R^5 together represent a C_1-C_4 alkylenedioxy group;

n is 1, 2, or 3;

W represents the $-CH_2-$, >CO, or CO-OR^6 group (in which R^6 represents any 1 of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

and pharmaceutically acceptable salts thereof.

2. A method of treating impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

3. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein Y and Z are oxygen.

4. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein W is $-CH_2-$.

5. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein n is 1.

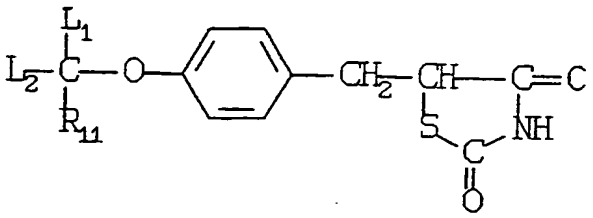
6. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein R_1, R_2, R_4, and R_5 are lower alkyl and R_3 is H.

7. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein Z and Y are oxygen, n is 1, and W is $-CH_2-$.

8. A method of Claim 2 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula I wherein the compound is (+)-5-[[4-[(3,4-dihydro-6-hydroxy-

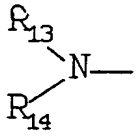
2,5,7,8-tetramethyl-2H-1-benxopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione.

9. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula II:



II

wherein R_{11} is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5- or 6-membered heterocyclic group including 1 or 2 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, or a group of the formula



wherein R_{13} and R_{14} are the same or different and each is lower alkyl or R_{13} and R_{14} are combined to each other either directly or as interrupted by a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur to form a 5- or 6-membered ring;

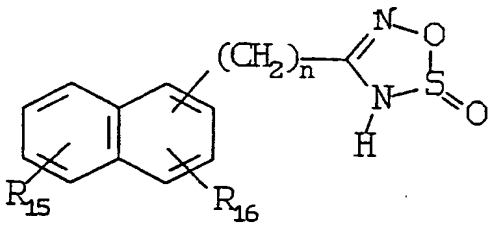
wherein R_{12} means a bond or a lower alkylene group; and
wherein L_1 and L_2 are the same or different and each is hydrogen or lower alkyl or L_1 and L_2 are combined to form an alkylene group, or a pharmaceutically acceptable salt thereof.

10. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering a therapeutically effective amount of a compound according to Claim 9 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

11. A method of Claim 10 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula II wherein the compound is pioglitazone.

12. A method of Claim 10 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula II wherein the compound is ciglitazone.

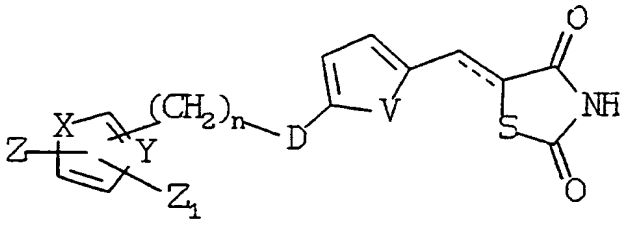
13. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula III:



III

wherein R_{15} and R_{16} are independently hydrogen, lower alkyl containing 1 to 6 carbon atoms, alkoxy containing 1 to 6 carbon atoms, halogen, ethynyl, nitrile, methylthio, trifluoromethyl, vinyl, nitro, or halogen substituted benzyloxy; n is 0 to 4 and the pharmaceutically acceptable salts thereof.

14. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula IV:

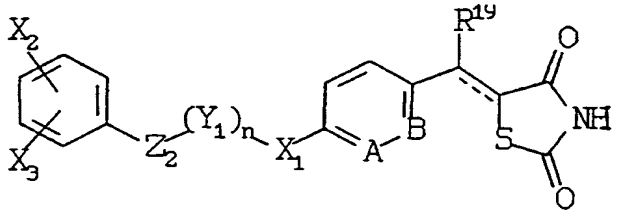


IV

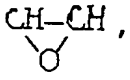
wherein the dotted line represents a bond or no bond;
V is -CH = CH-, -N = CH-, -CH = N- or S;
D is CH_2, CHOH, CO, C = NOR_{17} or CH = CH;
X is S, O, NR_{18}, -CH = N or -N = CH;
Y is CH or N;
Z is hydrogen, (C_1-C_7) alkyl, (C_3-C_7)cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, or phenyl

mono- or disubstituted with the same or different groups which are (C_1-C_3)alkyl, trifluoromethyl, (C_1-C_3)alkoxy, fluoro, chloro, or bromo;
Z' is hydrogen or (C_1-C_3)alkyl;
R_{17} and R_{18} are each independently hydrogen or methyl; and n is 1, 2, or 3;
the pharmaceutically acceptable cationic salts thereof; and the pharmaceutically acceptable acid addition salts thereof when the compound contains a basic nitrogen.

15. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula V:



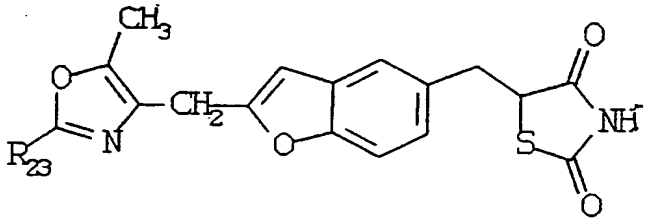
V

wherein the dotted line represents a bond or no bond;
A and B are each independently CH or N, with the proviso that when A or B is N, the other is CH;
X_1 is S, SO, SO_2, CH_2, CHOH, or CO;
n is 0 or 1;
Y_1 is CHR_{20} or R_{21}, with the proviso that when n is 1 and Y_1 is NR_{21}, X_1 is SO_2 or CO;
Z_2 is CHR_{22}, CH_2CH_2, CH=CH,  ,

OCH_2, SCH_2, $SOCH_2$ or SO_2CH_2;

R_{19}, R_{20}, R_{21}, and R_{22} are each independently hydrogen or methyl; and
X_2 and X_3 are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phenoxy, benzyloxy, bromo, chloro, or fluoro;
a pharmaceutically acceptable cationic salt thereof; or
a pharmaceutically acceptable acid addition salt thereof when A or B is N.

16. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula VI:

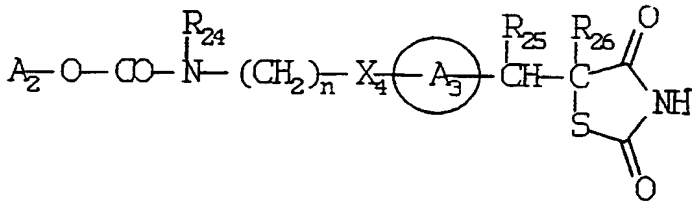


VI

or a pharmaceutically acceptable salt thereof wherein R_{23} is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl, or mono- or disubstituted phenyl wherein said substituents are independently alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 3 carbon atoms, halogen, or trifluoromethyl.

17. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective

amount of a compound of Formula VII:



VII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_2 represents an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

A_3 represents a benzene ring having in total up to 3 optional substituents;

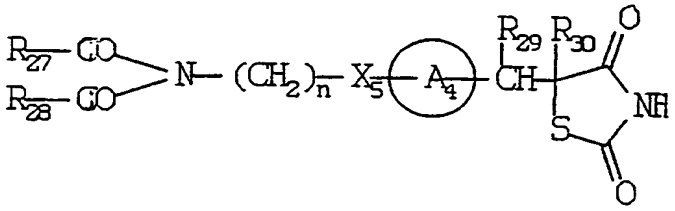
R_{24} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl, or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or A_2 together with R_{24} represents substituted or unsubstituted C_{2-3} polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

R_{25} and R_{26} each represent hydrogen, or R_{25} and R_{26} together represent a bond;

X_4 represents O or S; and

n represents an integer in the range of from 2 to 6.

18. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula VIII in unit dosage form



VIII

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate therefor, wherein:

R_{27} and R_{28} each independently represent an alkyl group, a substituted or unsubstituted aryl group, or an aralkyl group being substituted or unsubstituted in the aryl or alkyl moiety;

or R_{27} together with R_{28} represents a linking group, the linking group consisting of an optionally substituted methylene group and either a further optionally substituted methylene group or an O or S atom, optional substituents for the said methylene groups being selected from alkyl-, aryl, or aralkyl, or substituents of adjacent methylene groups together with the carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

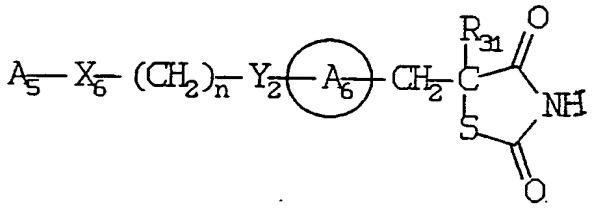
R_{29} and R_{30} each represent hydrogen, or R_{29} and R_{30} together represent a bond;

A_4 represents a benzene ring having in total up to 3 optional substituents;

X_5 represents O or S; and

n represents an integer in the range of from 2 to 6.

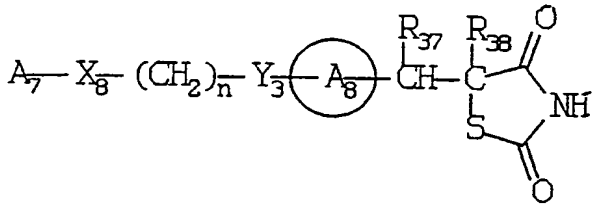
19. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula IX:



IX

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:
A_5 represents a substituted or unsubstituted aromatic heterocyclyl group;
A_6 represents a benzene ring having in total up to 5 substituents;
X_6 represents O, S, or NR_{32} wherein R_{32} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
Y_2 represents O or S;
R_{31} represents an alkyl, aralkyl, or aryl group; and
n represents an integer in the range of from 2 to 6.

20. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula X:



X

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A_7 represents a substituted or unsubstituted aryl group;

A_8 represents a benzene ring having in total up to 5 substituents;

X_8 represents O, S, or NR_{39} wherein R_{39} represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

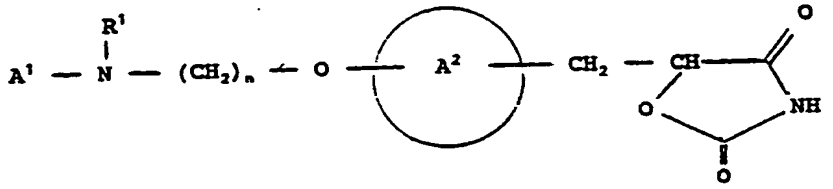
Y_3 represents O or S;

R_{37} represents hydrogen;

R_{38} represents hydrogen or an alkyl, aralkyl, or aryl group or R_{37} together with R_{38} represents a bond; and

n represents an integer in the range of from 2 to 6.

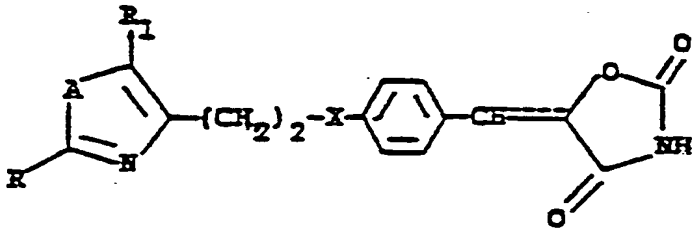
21. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula XI:



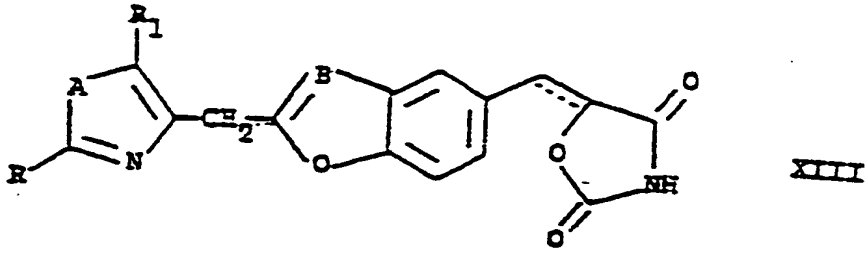
XI

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:
A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;
R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
A^2 represents a benzene ring having in total up to five substituents; and
n represents an integer in the range of from 2 to 6.

22. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound of Formula XII or XIII:



XII



XIII

or a pharmaceutically acceptable salt thereof wherein the dotted line represents a bond or no bond; R is cycloalkyl of three to seven carbon atoms, naphthyl, thienyl, furyl, phenyl or substituted phenyl wherein said substituent is alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms, trifluoromethyl, chloro, fluoro or bis(trifluoromethyl); R_1 is alkyl of one to three carbon atoms; X is O or C=O; A is O or S; and B is N or CH.

23. A method of treating impaired glucose tolerance to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering therefrom a therapeutically effective amount of a compound selected from the group consisting of

(+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl]methyl]-2,4-thiazolidinedione: (troglitazone);

4-(2-naphthylmethyl)-1,2,3,5-oxathiadiazole-2-oxide;

5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]-benzyl]-5-methylthiazolidine-2,4-dione;

5-[4-[2-[2,4-dioxo-5-phenylthiazolidin-3-yl)ethoxy]-benzyl]thiazolidine-2,4-dione;

5-[4-[2-[N-methyl-N-(phenoxycarbonyl)amino]ethoxy]-benzyl]thiazolidine-2,4-dione;

5-[4-(2-phenoxyethoxy)benzyl]thiazolidine-2,4-dione;

5-[4-[2-(4-chlorophenyl)ethylsulfonyl]benzyl]-thiazolidine-2,4-dione;

5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiazolidine-2,4-dione;

5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiadiazo-lidine-2,4-dione: (ciglitazone);

5-[[4-(3-hydroxy-1-methylcyclohexyl)methoxy]benzyl]-thiadiazolidine-2,4-dione;

5-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxyl]-benzyl]thiadizolidione-2,4-dione;

5-[4-[2-(5-ethylpyridin-2-yl)ethoxyl]benzyl]-thiadiazolidine-2,4- dione: (pioglitazone);

5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]-thiadiazoline-2,4-dione: (englitazone);

5-[[2-(2-naphthylmethyl)benzoxazol]-5-ylmethyl]-thiadiazoline-2,4-dione;

5-[4-[2-(3-phenylureido)ethoxyl]benzyl]thiadiazoline-2,4-dione;

5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]-benzy]thiadiazoline-2,4-dione;

5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]-benzyl]thiadiazoline-2,4-dione;

5-[2-(5-methyl-2-phenyloxazol-4-ylmethyl)-benzofuran-5-ylmethyl]- oxazolidine-2,4-dione;

5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]-benzyl]thiazolidine-2,4-dione; and

5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]-benzyl]-oxazolidine-2,4-dione.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10389

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/41, 31/42, 31/ 425, 31/44, 31/495, 31/505.
US CL :514/252, 256, 342, 360, 369, 375, 376.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/252, 256, 342, 360, 369, 375, 376.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, structure and "impared glucose tolerance"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,572,912 (YOSHIOKA ET AL.) 25 February 1986, columns 1 and 2.	1-8
X	US, A, 4,873,255 (YOSHIOKA ET AL) 10 October 1989, abstract.	1-8
X	US, A, 4,287,200 (KAWAMATSU ET AL) 01 September 1981, abstract.	9-12
X	US, A, 4,687,777 (MEGURO ET AL) 18 August 1987, abstract.	9-12
X	US, A, 4,897,405 (ALESSI ET AL.) 30 January 1990, column 1, line 49 to column 2, line 43.	13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 DECEMBER 1994	04 JAN 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD L. RAYMOND Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10389

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,061,717 (CLARK ET AL.) 29 October 1991, column 3, line 54 to column 4, line 63.	15
X	US, A, 5,132,317 (CANTELLO ET AL.) 21 January 1992, column 1, lines 18-58.	20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10389

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10389

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I Claims 1-8 drawn to treating diabetes in a host employing the compound of Formula I.

Group II Claims 9-12 drawn to treating diabetes in a host employing the compound of Formula II.

Group III Claim 13 drawn to treating diabetes in a host employing the compound of Formula III.

Group IV Claim 14 drawn to treating diabetes in a host employing the compound of Formula IV

Group V Claim 15 drawn to treating diabetes in a host employing the compound of Formula V

Group VI Claim 16 drawn to treating diabetes in a host employing the compound of Formula VI

Group VII Claim 17 drawn to treating diabetes in a host employing the component of formula VII

Group VIII Claim 18-20 drawn to treating diabetes in a host employing the compound of Formula VIII

Group IX Claim 21 drawn to treating diabetes in a host employing the compound of Formula XI
Group X Claim 22 drawn to treating diabetes in a hostemployingthe compound of Formula XII

Group XI Claim 22 drawn to treating diabetes in a host employing the compound of Formula XIII

Claim 23 will be examined with the elected invention as it reads on the specific Group.
Lack of unity of invention has been found to exist because the broad spectrum of compounds contained in the 23 involved claims are diverse in core structure, or are not among art recognized equivalents.